**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of :

Johannes PLATZEK et al. : Examiner: Wells

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For: **GALENICAL FORMULATIONS**

**DECLARATION UNDER 37 C.F.R. §1.132**

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Dr. Bernd Misselwitz, being duly warned, declare that:

I am a citizen of Germany, residing at Metzer Straβe 4, 16548 Glienicke, Germany.

I possess the degree of Doctor of Natural Sciences, having studied Pharmacy at the "Ernst-Moritz-Arndt-Universitaet" in Greifswald.

I am a member of the Germany Society of Pharmacology and Toxicology.

Since May 1996, I have been employed as a pharmacist by Schering Aktiengesellschaft, Berlin, Germany, and I am presently head of a research group for the pharmacology of contrast media.

Under my supervision, the following experiments were conducted in the Laboratories of Schering Aktiengesellschaft.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made

are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

28/10/04
Date

Dr. Bernd Misselwitz

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Dr. B. Misselwitz; MRI and X-Ray Research; Tel.: 468-17862 12/10/2002

**Additional Embodiments for Substantiating the Advantage of Mixed Micelles Compared to the Individual Compound:**

**Example 1: Relaxivity**

The T1 and T2 relaxation times of plasma with increasing concentrations of MRT contrast media (0.05 to 0.25 mmol of Gd/l) were measured at 0.47 T and at a temperature of 40°C with use of an NMR pulse spectrometer (Minispec PC 20; Bruker, Rheinstetten, Germany).

The T1 and T2 relaxation times of a galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and **3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid** (proportion of 20 mol%) were considerably higher compared to pure **complex I**.

| Substance | Medium | Relaxivity [l/(mmol*s)] | |
|---|---|---|---|
| | | R1 | R2 |
| Galenical formulation that consists of complex I and 3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid | Plasma | 32.7 | 42.4 |
| Complex I | Plasma | 28.2 | 33.0 |

**Example 2: Organ Distribution After Intravenous Administration of the Contrast Medium in Prostate-Cancer-Bearing Rats**

After intravenous administration of 200 μmol of total gadolinium/kg of body weight of a galenical formulation that consists of **complex III** (Gd-GlyMe-DOTA-trimer-perfluorooctyl-oxadecylamide) and the **compound of Example 11a** (mannose-perfluorooctylsulfonamide; proportion 40 mol %) in rats (Cop-inbreeding Dunning R3327 MAT-Lu prostate cancer i.m.-implanted 12 days earlier), the metal content in the entire organism was determined 24 hours after administration (MW ± SD, n = 3). The galenical formulation in this case has a smaller Gd content (8.3% of the administered dose) compared to the pure **complex III** (9.2% of the administered dose), i.e., the galenical formulation is better eliminated from the body.

**Example 3: Signal Increase (Enhancement) in Healthy Lymph Node Tissue by Means of MRT After Intravenous Administration of the Contrast Medium in Guinea Pigs**

The table shows the enhancement (percentage of signal increase in comparison to the precontrast value) that was achieved by means of MRT in popliteal, inguinal and iliac lymph nodes at the time of 60 minutes after intravenous administration of 100 μmol of Gd/kg of body weight of a galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and the **compound of Example 11a** (mannose-perfluorooctylsulfonamide; proportion of 40 mol %), as well as a galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and **3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid** (proportion of 40 mol %), in comparison to the pure **complex I** in guinea pigs with stimulated lymph nodes (complete Freund adjuvant; in each case 0.1 ml i.m. in the right and left upper and lower legs; 2 weeks before the administration of test substance) (MW ± SD, n = 3). In this experiment, a clear advantage of the galenical formulations in comparison to the pure complex was also shown.

| Substance | Enhancement [%] in Lymph Nodes 60 minutes p.i. | | |
|---|---|---|---|
| | **Popliteal** | **Inguinal** | **Iliac** |
| Complex I | 107 ± 14 | 117 ± 36 | 88 ± 9 |
| Galenical formulation that consists of complex I and a compound of Example 11a | 170 ± 38 | 123 ± 20 | 122 ± 13 |
| Galenical formulation of complex I and 3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid | 195 ± 26 | 141 ± 14 | 148 ± 25 |

**Example 4: Lymph Node Concentration in Guinea Pigs After Interstitial Administration**

A galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and the **compound of Example 11** (mannose-perfluorooctylsulfonamide; proportion of 40 mol %) as well as the pure **complex I** were

studied 30 minutes after subcutaneous administration (10 μmol of total gadolinium/kg of body weight, hind paw s.c.) in guinea pigs with stimulated lymph nodes (complete Freund adjuvant; in each case 0.1 ml i.m. in the right and left upper and lower legs; 2 weeks before administration of the test substance) with respect to their lymph node concentration in three successive lymph node stations (popliteal, inguinal, iliac). In this connection, the results listed below (determination of the gadolinium concentration by means of ICP-AES, MW ± SD, n =3) were obtained:

| | **Gd Content in [% of Dose/g of Tissue] 30 minutes p.i.** | | |
|---|---|---|---|
| | **Popliteal** | **Inguinal** | **Iliac** |
| Galenical formulation that consists of complex I and a compound from Example 11a | 48.1 ± 13.2 | 23.1 ± 8.8 | 20.1 ± 7.7 |
| Complex I | 28.7 ± 1.6 | 11.4 ± 1.0 | 13.4 ± 4.2 |